PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 July 2000 (28.07.00)	
International application No. PCT/EP99/09660	**Applicant's or agent's file reference** P71419WO
International filing date (day/month/year) 07 December 1999 (07.12.99)	**Priority date** (day/month/year) 07 December 1998 (07.12.98)
Applicant DONG, Zheng, Xin	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 May 2000 (22.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

EP9909660

PATENT COOPERATION TREATY

M9L

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
LUNT, Mark George Franc
DIBB LUPTON ALSOP
Fountain Precinct
Balm Green
Sheffield S1 1RZ
GRANDE BRETAGNE

ENTERED BY .....

- 3 JAN 2001

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	27.12.2000
Applicant's or agent's file reference: P71419WO	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/09660	07/12/1999	07/12/1998

International Patent Classification (IPC) or both national classification and IPC
C07K14/605

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET...et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items: Due 27 feb 2001

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/04/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Rojo Romeo, E

Formalities officer (incl. extension of time limits)
Sülberg, A
Telephone No. +49 89 2399 7548

PATENT COOPERATION TREATY

MGL

30537-186 WO1

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUNT, Mark George Franc
DIBB LUPTON ALSOP
Fountain Precinct
Balm Green
Sheffield S1 1RZ
GRANDE BRETAGNE

ENTERED BY .....

- 2 MAR 2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28.02.2001
Applicant's or agent's file reference P71419WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/09660	07/12/1999	07/12/1998

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET...et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Emslander, S Tel.+49 89 2399-8718

Form PCT/IPEA/416 (July 1992)

MGL

PATENT COOPERATION TRE. Y

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
LUNT, Mark George Franc
DIBB LUPTON ALSOP
Fountain Precinct
Balm Green
Sheffield S1 1RZ
GRANDE BRETAGNE

ENTERED BY .....
- 5 IAN 2001

INVITATION TO PAY PROTEST FEE

(PCT Rule 68.3(e))

Date of mailing *(day/month/year)*	03.01.01
Applicant's or agent's file reference: P71419WO	**PAYMENT DUE** within **ONE MONTH** from the above date of mailing
International application No.: PCT/EP 99/09660	International filing date *(day/month/year)*: 07/12/1999

Applicant: SOCIETE DE CONSEILS DE RECHERCHES ET...et al.

1. The applicant is **invited,** within the time limit indicated above, **to pay a protest fee** for the examination of the protest, in the amount of:

EUR 1.022,- *(amount/currency)*

since a prior review of the justification for the invitation to pay additional fees (Form PCT/IPEA/405) has resulted in the requirement of payment of additional fees to be upheld for the following reason(s):

see following two pages

DUE
3 feb 2001

1 file to ML

2. **Failure to pay** the protest fee within the time limit indicated above will result in the protest being withdrawn.

Name and mailing address of the IPEA/
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer
A. Sülberg

Summary of facts and submissions

1. Further to a partial Search Report dated 25.05.00 informing the Applicant that the application did not comply with the requirements of Rule 13.1-13.3 PCT and concerned six different inventions, the Applicant payed three additional search fees (letter of 07.07.00) so as to have inventions 1-4 (see below) be searched. An International Search Report was issued on 16.08.00.

2. The IPEA agreed with the unity objection raised by the ISA and issued a form PCT/IPEA/405 (see annex) on 19.10.00 informing the Applicant that the application did not comply with the requirements of Rule 13.1-13.3 PCT and concerned four different inventions.

3. In response, the Applicant paid three further examination fees under protest.

Results of prior review

1. Under Rule 68.3(e), first sentence, PCT, when additional fees are paid under protest, the case must be subject to "a prior review of the justification for the invitation to pay additional fees".
   In other words, the matter to be decided is the correctness of the original opinion regarding the question of lack of unity.

2. In his letter dated 20.11.00, the Applicant submits that the subject-matter of the four inventions are linked by the single inventive concept that the disclosed GLP-1 analogues have improved ability to form amide bonds at residues located near the carboxyl terminal end (i.e. at positions 35 and 36).

   The common inventive concept indicated by the Applicant is not to be found, or even suggested, anywhere in the present application and thus, cannot be accepted. The problem underlying the present application and stated at page 2 of the specification, concerns the metabolic instability of GLP-1 in vivo, exogenously administered GLP-1 being rapidly degraded. Thus the need for GLP-1 analogues which are metabolically more stable than native GLP-1. Since such analogues were known from prior art, the objection for unity raised in form PCT/IPEA/405 has been found by the review panel to be justified. The reasons for the objections are given in said form (see annex).

3. The Applicant is therefore invited to pay a protest fee (Rule 68.3(e) PCT), should he desire further examination of the protest made (pursuant to Rule 68.3(c) PCT).

For the review panel

E. Rojo Romeo

P. Juliá

C. Gugerell

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
DIBB LUPTON ALSOP
Attn. LUNT, Mark George Franc
Fountain Precinct
Balm Green
Sheffield S1 1RZ
UNITED KINGDOM

ENTERED BY .....

25 AUG 2000

Date of mailing (day/month/year) 22/08/2000	
Applicant's or agent's file reference P71419WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 99/09660	International filing date (day/month/year) 07/12/1999

Applicant

SOCIETE DE CONSEILS DE RECHERCHES ET...et al.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. ***Further action(s):*** *The applicant is reminded of the following:*

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Renate Jordan

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually *no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published* for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered *as having been received on time if they are received by the International Bureau after the expiration of the* applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of *one or more of the claims as filed.*

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or *in addition to, the translation of the claims as filed.*

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P71419WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/09660	07/12/1999	07/12/1998
Applicant		
SOCIETE DE CONSEILS DE RECHERCHES ET...et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/09660

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-8, 11-17 incompletely
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-18, all partially

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18, all partially

Compounds of formula 1, restricted (see box 3, form 206 in annex) to the compounds of examples 1-3, 5-14, 24, 26, 27, 29, 45, 78, 136, 364, 365, 370-373, 395-404, characterized by having an alpha-aminobutyric acid residue at positions 8 and 35.

2. Claims: 1-18, all partially

Compounds of formula 1, restricted (see box C, form 206 in annex) to the compounds of examples 4, 51, 366-369, 374, 377, 379-382, 384-391, 393, 394, 405-411 characterized by having an alpha-aminobutyric acid residue at position 8 and a beta-alanine residue at position 35.

3. Claims: 1-8, 11-18, all partially

Compounds of formula 1, restricted (see box C, form 206 in annex) to the compound of example 383, characterized by having an alpha-aminobutyric acid residue at position 8 and a D-arginine residue at position 36.

4. Claims: 1-8, 11-18, all partially

Compounds of formula 1, restricted (see box C, form 206 in annex) to the compound of example 292, characterized by having an alpha-aminobutyric acid residue at position 8 and a D-arginine residue at position 35.

5. Claims: 1-8, 11-18, all partially

Compounds of formula 1, restricted (see box C, form 206 in annex) to the compounds of examples 375 and 378, characterized by having an glycine residue at position 8.

6. Claims: 1-8, 11-18, all partially

Compounds of formula 1, restricted (see box C, form 206 in annex) to the compound of example 376, characterized by having a serine residue at position 8.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8, 11-17 incompletely

Present claims 1-8, 11-17 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely those compounds for which the synthesis has been described (i.e examples 1-14, which is the subject-matter of claims 9 and 10, and examples 366 to 369) or for which physical data has been given (i.e compounds mentioned in Table 1).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PATENT COOPERATION TREATY

PCT

REC'D 02 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

14

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P71419WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/09660	07/12/1999	07/12/1998
International Patent Classification (IPC) or national classification and IPC C07K14/605		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET...et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/05/2000	28.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rojo Romeo, E Telephone No. +49 89 2399 7321

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09660

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-42 as originally filed

Claims, No.:

1-18 as originally filed

Sequence listing part of the description, pages:

1-183, filed with the letter of 22.03.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-8, 11-18 (partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-8, 11-18 (partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

☒ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 9, 10 (entirely); 1-8, 11-18 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-11, 15-18
	No:	Claims	12-14

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of this report

A sequence listing (pages 1-181) was filed with the present application which contains SEQ ID NO: 1 to 363.

No answer to the Written Opinion was filed by the Applicant. The present Report is thus based on said Written Opinion.

The Applicant did not pay the protest fee.

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As stated in the International Search Report, present claims 1-8 and 11-17 relate to an extremely large number of possible compounds. Consequently, the search was carried out for those parts of the application which do appear to be clear (and or concise), namely those compounds for which the synthesis has been described (i.e. examples 1-14, which is the subject-matter of claims 9 and 10 and examples 366 to 369) or for which physical data has been given (i.e., compounds mentioned in Table 1).

According to Rule 66.1(e) PCT, International Preliminary Examination is carried out on the searched subject-matter, i.e. on claims 9 and 10 (totally) and on claims 1-8 and 11-17 (partially) as far as they concern the compounds mentioned above.

Any other subject-matter is, therefore, disregarded.

R Item IV

Lack of unity of invention

The International Preliminary Examination Authority agrees with the objection for lack of unity raised by the International Search Authority. The ISA found the current application to concern 6 different inventions. Search fees were payed for 4 inventions (1-4) which were searched.

This international application concerns 4 different inventions, namely:

1. Claims 1-18, all partially

   Compounds of formula 1, restricted to the compounds of examples 1-3, 5-14, 24, 26, 27, 29, 45, 78, 136, 364, 365, 370-373, 395-404, characterized by having an alpha-amino butyric acid residue at positions 8 and 35.

2. Claims 1-18, all partially

Compounds of formula 1, restricted to the compounds of examples 4, 51,366-369, 374, 377, 379-382, 384-391, 393, 394, 405-411, characterized by having an alpha-amino butyric acid residue at position 8 and a beta-alanine residue at position 35.

3. Claims 1-18, all partially

Compounds of formula 1, restricted to the compound of example 383, characterized by having an alpha-amino butyric acid residue at position 8 and a D-arginine residue at position 36.

4. Claims 1-18, all partially

Compounds of formula 1, restricted to the compound of example 292, characterized by having an alpha-amino butyric acid residue at position 8 and a D-arginine residue at position 35.

The problem underlying the present application is to provide glucagon-like peptide-1 (GLP-1) analogues that are more active or more metabolically stable than the native GLP-1. The solution to this problem is a compound characterized by formula 1.

GLP-1 analogues having improved activity and stability have been disclosed in the prior art, see WO9111457 (e.g. abstract, page 4, line 11-page 7, line 7). Moreover, the parent compound falls under the scope of formula 1 (i.e. if R1 is OH or NH2 and R2 and R3 are both hydrogen).

In view of the prior art, the common concept linking the claimed compounds is not new, and the problem of the present application can be redefined as the provision of additional GLP-1 analogues having improved activity and stability. The different solutions to this problem being the compounds of the inventions 1-4 identified above.

With regard to the regrouping of the compounds into different groups, the following should be noted. Since the Applicant did not disclose which structural feature(s) of formula 1 specify the contribution of the present compounds over the prior art, i.e. which feature(s) can be regarded as a special technical feature in the sense of Rule 13(2) PCT, these had to be deduced from the exemplified compounds. Among the compounds which were considered searchable, a first subdivision can be made in compounds having an alpha-

amino butyric acid residue at position 8 and those not having an alpha-amino butyric acid residue at this position.
However, since GLP-1 analogues having an alpha-amino butyric acid residue at position 8 are already known in the prior art, see WO9111457, page 25, lines 17-22, this feature cannot be regarded as a special technical feature in the sense of Rule 13(2) PCT and thus, the group of inventions has been further subdivided into 4 groups (inventions 1-4).

In conclusion, due to the fact that GLP-1 analogues having an increased activity and stability and having an alpha-amino butyric acid residue at position 8 have already been disclosed, and due to the fact that no other technical features can be distinguished which, in the light of the prior at could be regarded as special technical features in the sense of Rule 13(2) PCT, the IPEA is of the opinion that there is no single inventive concept underlying te compounds of the present application in the sense of Rule 13(1) PCT. Consequently, there is lack of unity and the different compounds, not belonging to a common inventive concept, are formulated as the different inventions above.

The Applicant has payed three additional examination fees.
Consequently, all four inventions or groups of inventions mentioned above are examined here.

Re Item V

R asoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive t p or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents cited in the International Search Report:

D1: WO 98 19698 A (LILLY CO ELI) 14 May 1998 (1998-05-14)

D2: WO 91 11457 A (BUCKLEY DOUGLAS I ;HABENER JOEL F (US); MALLORY JOANNE B (US); MOJ) 8 August 1991 (1991-08-08)

D1 discloses hGLP-1 analogues and derivatives and their use in the regulation of obesity.
D2 discloses hGLP-1 analogues and their use in the treatment of diabetes

1. Novelty (Art. 33(2) PCT)
   In view of the currently available prior art, the current set of claims, as far as they concern the searched compounds of inventions 1-4 (for which the synthesis has been described (i.e. examples 1-14, which is the subject-matter of claims 9 and 10 and

examples 366 to 369) or for which physical data has been given (i.e., compounds mentioned in Table 1)), are novel over the available prior art (e.g. D1 and D2).

2. Inventive step (Art. 33(3) PCT)

Concerning inventions 1-4, the problem underlying the present application is the provision of glucagon-like peptide-1 (GLP-1) analogues that are more active or more metabolically stable than the native GLP-1. The solutions provided by the present application are the compounds of inventions 1-4. The Applicant fails, however, to provide evidence of the claimed activity for any of the compounds examined. In the absence of evidence that the claimed compounds have any advantage over other hGLP-1 analogues disclosed in prior art, the claimed hGLP-1 analogues constitute "compounds" with no technically useful property. In this case, any prior art compound identifiable as a hGLP-1 analogue, regardless of its technical properties, is equally suitable as the starting point for making structural modifications and may be considered to represent the closest prior art. Without the concomitant need to provide any particular technical effect, for the skilled person, any putative hGLP-1 analogue may provide an equally obvious solution. Thus, inventive activity cannot be acknowledged for any of the compounds of inventions 1-4.

The Applicant's attention is drawn to the fact that the use of hGLP-1 analogues in the treatment of disease (e.g. diabetes, see D2) is known from prior art. Consequently, claims 12-14, 17 and 18 could still be objected for lack of inventive step.

Consequently, claims 1-18 lack inventive activity.

3. Industrial applicability (Art. 33(4) PCT)

For the assessment of the present claim 12-14, on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

In SEQ ID NO: 1, the numbering of the amino acids does not comply with the numbering found in prior art and suggested in the rest of the present application (i.e. His 1 being actually amino acid 7).

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)

1.1 The Applicant's attention is drawn to the fact that the current set of claims does not refer to a particular sequence to define the term hGLP-1. In the absence of a reference to a concrete sequence characterizing the hGLP-1 peptide (i.e. SEQ ID NO: 1), said claims lack technical features necessary to clearly define the claimed-subject-matter since the term hGLP-1 has no technical meaning for the person skilled in the art. Consequently, the current set of claims may be interpreted as being directed to any protein or polynucleotide.

Relating to this, the Applicant's attention is drawn to the fact that the claims must be clear without the context of the application.

Concerning this, the Applicant's attention is drawn to the fact that the abbreviations of the different substituents are not defined in the claims (e.g. Aib, A6c...).

1.2 Concerning claim 11, the Applicant's attention is drawn to the fact that the intention of use does not limit the scope of a claim which is directed to a composition. The claim must be interpreted as being directed to a composition per se regardless of its use. No unified criteria exist in the PCT as far as first medical use is concerned. The EPO, for instance, will allow claims in a form such as:"substance or composition X", followed by the indication of use ("for use as a medicament"). Thus, claim 11 is directed to the product of claim 1.

1.3 The wording of claim 12 is unclear, since the skilled person would not know which one of the agonist effects of hGLP-1 are concerned, neither what a "person in need of said agonist effect" may suffer from.

2. Support by specification (Art. 6 PCT), in combination with Art. 5 PCT (complete and enabling disclosure)

2.1 The Applicant fails to provide any evidence that the claimed compounds may indeed

be used in the treatment of disease. Claims 12-14, 17 and 18 are based on mere speculation from prior art, and thus, not supported by the specification.

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

   Description, pages:

   1-42 as originally filed

   Claims, No.:

   1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-8, 11-18 (partially),

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-8, 11-18 (partially).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☒ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 9, 10 (entirely); 1-8, 11-18 (partially).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-18
Industrial applicability (IA)	Claims	12-14

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of th opinion

A sequence listing (pages 1-181) was filed with the present application which contains SEQ ID NO: 1 to 363.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As stated in the International Search Report, present claims 1-8 and 11-17 relate to an extremely large number of possible compounds. Consequently, the search was carri d out for those parts of the application which do appear to be clear (and or concise), namely those compounds for which the synthesis has been described (i.e. examples 1-14, which is the subject-matter of claims 9 and 10 and examples 366 to 369) or for which physical data has been given (i.e., compounds mentioned in Table 1).

According to Rule 66.1(e) PCT, International Preliminary Examination is carried out on the s arched subject-matter, i.e. on claims 9 and 10 (totally) and on claims 1-8 and 11-17 (partially) as far as they concern the compounds mentioned above.

Any other subject-matter is, therefore, disregarded.

R Item IV

Lack of unity of invention

The International Preliminary Examination Authority agrees with the objection for lack of unity raised by the International Search Authority. The ISA found the current application to concern 6 different inventions. Search fees were payed for 4 inventions (1-4) which were searched.

This international application concerns 4 different inventions, namely:

1. Claims 1-18, all partially

   Compounds of formula 1, restricted to the compounds of examples 1-3, 5-14, 24, 26, 27, 29, 45, 78, 136, 364, 365, 370-373, 395-404, characterized by having an alpha-amino butyric acid residue at positions 8 and 35.

2. Claims 1-18, all partially

   Compounds of formula 1, restricted to the compounds of examples 4, 51,366-369, 374, 377, 379-382, 384-391, 393, 394, 405-411, characterized by having an alpha-

amino butyric acid residue at position 8 and a beta-alanine residue at position 35.

3. Claims 1-18, all partially

Compounds of formula 1, restricted to the compound of example 383, characterized by having an alpha-amino butyric acid residue at position 8 and a D-arginine residue at position 36.

4. Claims 1-18, all partially

Compounds of formula 1, restricted to the compound of example 292, characterized by having an alpha-amino butyric acid residue at position 8 and a D-arginine r sidue at position 35.

The problem underlying the present application is to provide glucagon-like peptide-1 (GLP-1) analogues that are more active or more metabolically stable than the native GLP-1. The solution to this problem is a compound characterized by formula 1.

GLP-1 analogues having improved activity and stability have been disclosed in the prior art, see WO9111457 (e.g. abstract, page 4, line 11-page 7, line 7). Moreover, the parent compound falls under the scope of formula 1 (i.e. if R1 is OH or NH2 and R2 and R3 ar both hydrogen).

In view of the prior art, the common concept linking the claimed compounds is not new, and the problem of the present application can be redefined as the provision of additional GLP-1 analogues having improved activity and stability. The different solutions to this problem being the compounds of the inventions 1-4 identified above.

With regard to the regrouping of the compounds into different groups, the following should be noted. Since the Applicant did not disclose which structural feature(s) of formula 1 specify the contribution of the present compounds over the prior art, i.e. which feature(s) can be regarded as a special technical feature in the sense of Rule 13(2) PCT, these had to be deduced from the exemplified compounds. Among the compounds which were considered searchable, a first subdivision can be made in compounds having an alpha-amino butyric acid residue at position 8 and those not having an alpha-amino butyric acid residue at this position.
However, since GLP-1 analogues having an alpha-amino butyric acid residue at position

8 are already known in the prior art, see WO9111457, page 25, lines 17-22, this feature cannot be regarded as a special technical feature in the sense of Rule 13(2) PCT and thus, the group of inventions has been further subdivided into 4 groups (inventions 1-4).

In conclusion, due to the fact that GLP-1 analogues having an increased activity and stability and having an alpha-amino butyric acid residue at position 8 have already been disclosed, and due to the fact that no other technical features can be distinguished which, in the light of the prior at could be regarded as special technical features in the sense of Rule 13(2) PCT, the IPEA is of the opinion that there is no single inventive concept underlying te compounds of the present application in the sense of Rule 13(1) PCT. Consequently, there is lack of unity and the different compounds, not belonging to a common inventive concept, are formulated as the different inventions above.

The Applicant has payed three additional examination fees.
Consequently, all four inventions or groups of inventions mentioned above are examined here.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents cited in the International Search Report:

D1: WO 98 19698 A (LILLY CO ELI) 14 May 1998 (1998-05-14)

D2: WO 91 11457 A (BUCKLEY DOUGLAS I ;HABENER JOEL F (US); MALLORY JOANNE B (US); MOJ) 8 August 1991 (1991-08-08)

D1 discloses hGLP-1 analogues and derivatives and their use in the regulation of obesity.
D2 discloses hGLP-1 analogues and their use in the treatment of diabetes

1. Novelty (Art. 33(2) PCT)
   In view of the currently available prior art, the current set of claims, as far as they concern the searched compounds of inventions 1-4 (for which the synthesis has been described (i.e. examples 1-14, which is the subject-matter of claims 9 and 10 and examples 366 to 369) or for which physical data has been given (i.e., compounds mentioned in Table 1)), are novel over the available prior art (e.g. D1 and D2).

2. Inventive step (Art. 33(3) PCT)

Concerning inventions 1-4, the problem underlying the present application is the provision of glucagon-like peptide-1 (GLP-1) analogues that are more active or more metabolically stable than the native GLP-1. The solutions provided by the present application are the compounds of inventions 1-4. The Applicant fails, however, to provide evidence of the claimed activity for any of the compounds examined. In th absence of evidence that the claimed compounds have any advantage over other hGLP-1 analogues disclosed in prior art, the claimed hGLP-1 analogues constitute "compounds" with no technically useful property. In this case, any prior art compound identifiable as a hGLP-1 analogue, regardless of its technical properties, is equally suitable as the starting point for making structural modifications and may be considered to represent the closest prior art. Without the concomitant need to provide any particular technical effect, for the skilled person, any putative hGLP-1 analogue may provide an equally obvious solution. Thus, inventive activity cannot be acknowledged for any of the compounds of inventions 1-4.

The Applicant's attention is drawn to the fact that the use of hGLP-1 analogues in the treatment of disease (e.g. diabetes, see D2) is known from prior art. Consequently, claims 12-14, 17 and 18 could still be objected for lack of inventive step.

Consequently, claims 1-18 lack inventive activity.

3. Industrial applicability (Art. 33(4) PCT)

For the assessment of the present claim 12-14, on the question wheth r it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

R Item VII

Certain defects in the international application

In SEQ ID NO: 1, the numbering of the amino acids does not comply with the numbering found in prior art and suggested in the rest of the present application (i.e.

His 1 bing actually amino acid 7).

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)

1.1 The Applicant's attention is drawn to the fact that the current set of claims does not refer to a particular sequence to define the term hGLP-1. In the absence of a reference to a concrete sequence characterizing the hGLP-1 peptide (i.e. SEQ ID NO: 1), said claims lack technical features necessary to clearly define the claimed-subject-matter since the term hGLP-1 has no technical meaning for the person skilled in the art. Consequently, the current set of claims may be interpreted as b ing directed to any protein or polynucleotide.
Relating to this, the Applicant's attention is drawn to the fact that the claims must be clear without the context of the application.
Concerning this, the Applicant's attention is drawn to the fact that the abbreviations of the different substituants are not defined in the claims (e.g. Aib, A6c...).

1.2 Concerning claim 11, the Applicant's attention is drawn to the fact that the intention of use does not limit the scope of a claim which is directed to a composition. The claim must be interpreted as being directed to a composition per se regardless of its use. No unified criteria exist in the PCT as far as first medical use is concerned. The EPO, for instance, will allow claims in a form such as:"substance or composition X", followed by the indication of use ("for use as a medicament"). Thus, claim 11 is directed to the product of claim 1.

1.3 The wording of claim 12 is unclear, since the skilled person would not know which one of the agonist effects of hGLP-1 are concerned, neither what a "person in need of said agonist effect" may suffer from.

2. Support by specification (Art. 6 PCT), in combination with Art. 5 PCT (complete and enabling disclosure)

2.1 The Applicant fails to provide any evidence that the claimed compounds may indeed be used in the treatment of disease. Claims 12-14, 17 and 18 are based on mere speculation from prior art.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07K 14/605, A61K 38/26

A2

(11) International Publication Number: WO 00/34331

(43) International Publication Date: 15 June 2000 (15.06.00)

(21) International Application Number: PCT/EP99/09660

(22) International Filing Date: 7 December 1999 (07.12.99)

(30) Priority Data:

09/206,601	7 December 1998 (07.12.98)	US
60/111,255	7 December 1998 (07.12.98)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: ANALOGUES OF GLP–1

(57) Abstract

The present invention is directed to peptide analogues of glucagon–like peptide–1, the pharmaceutically–acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ANALOGUES OF GLP-1

Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J.M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M.K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulphonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G.G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against s vere

hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C, Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefevbre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diagbetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),

(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, ß-Nal, Cha, Trp or X^1-Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, ß-Nal or X^1-Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1-Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, Pal, ß-Nal, X^1-Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, ß-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X^1-Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or X^1-Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is Gly, ß-Ala, D-Ala, Gaba, Ava, HN-$(CH_2)_m$-C(O), Aib, Acc or a D-amino acid;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

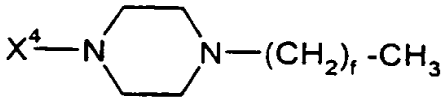
A^{37} is Gly, ß-Ala, Gaba, Ava, Aib, Acc, Ado, Arg, Asp, Aun, Aec, HN-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), a D-amino acid, or deleted;

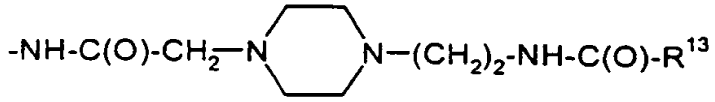
A^{38} is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) Ava, Ado, Aec or deleted;

A^{39} is D- or L-Lys, D- or L-Arg, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), Ava, Ado, or Aec;

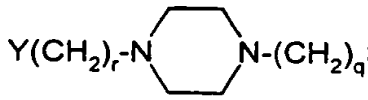
X^1 for each occurrence is independently selected from the group consisting of (C_1-C_6)alkyl, OH and halo;

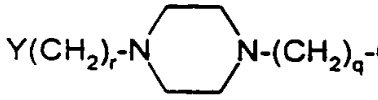
R^1 is OH, NH_2, (C_1-C_{30})alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a (C_1-C_{12})hydrocarbon moiety, and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is 



or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is , (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, C(O)X^5,  , or



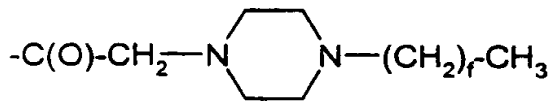
; wherein Y is H, OH or NH_2; r is 0 to 4; q is 0 to 4; and X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl or hydroxynaphthyl(C_1-C_{30})alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, (C_1-C_{30})alkyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, –C((NH)(NH_2)) or



; and

R^{12} and R^{13} each is, independently for each occurrence, (C_1-C_{30})alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or

, then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not ($Arg^{26,34}$, Lys^{38})hGLP-1(7-38)-E, (Lys^{26}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, (Lys^{34}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, ($Lys^{26,34}$-bis(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, (Arg^{26}, Lys^{34}(N_ε-alkanoyl))hGLP-1(8-36, -37 or -38)-E, ($Arg^{26,34}$, Lys^{38}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E or ($Arg^{26,34}$, Lys^{38}(N_ε-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or -NH_2;

(iv) a compound of formula (I) is not Z^1-hGLP-1(7-36, -37 or -38)-OH, Z^1-hGLP-1(7-36, -37 or -38)-NH_2, wherein Z^1 is selected from the group consisting of:

(a) (Arg^{26}), (Arg^{34}), ($Arg^{26,34}$), (Lys^{36}), (Arg^{26}, Lys^{36}), (Arg^{34}, Lys^{36}), (D-Lys^{36}), (Arg^{36}), (D-Arg^{36}), ($Arg^{26,34}$, Lys^{36}) or ($Arg^{26,36}$, Lys^{34});

(b) (Asp^{21});

(c) at least one of (Aib^8), (D-Ala^8) and (Asp^9); and

(d) (Tyr^7), (N-acyl-His^7), (N-alkyl-His^7), (N-acyl-D-His^7) or (N-alkyl-D-His^7);

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not (N-Me-Ala^8)hGLP-1(8-36 or -37), (Glu^{15})hGLP-1(7-36 or -37), (Asp^{21})hGLP-1(7-36 or -37) or (Phe^{31})hGLP-1(7-36 or -37)

or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing compound is where A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe or ß-Nal; or a pharmaceutically acceptable salt thereof.

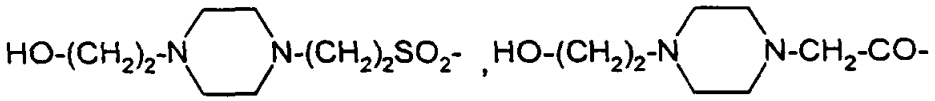
A preferred group of compounds of the immediately foregoing group of compounds is wher A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, ß-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr or ß-Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib

or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O); A^{28} is Phe or ß-Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

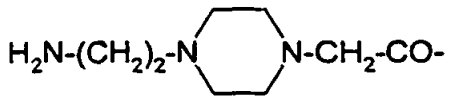
A preferred group of compounds of the immediately foregoing group of compounds is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c, D-Arg or Gly; and A^{37} is Gly, Aib, ß-Ala, Ado, D-Ala Ava, Asp, Aun, D-Asp, D-Arg, Aec, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or deleted; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

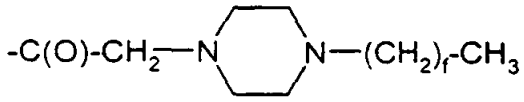
A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R^2 is H and R^3 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl,



or

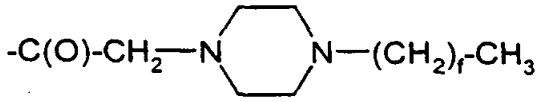


A preferred compound of the formula (I) is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c D-Arg or Gly; and A^{37} is Gly, Aib, ß-Ala, Ado, D-Ala, Ava, Asp, Aun, D-Asp, D-Arg, Aec, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or



, and R^{11} is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alkylsulfonyl or



, or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula:

$(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$,

$((N_\alpha\text{-HEPES-His})^7, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$,

$((N_\alpha\text{-HEPA-His})^7, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^8, \beta\text{-}Ala^{35})hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26}, Lys^{34}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}38)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-decanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-dodecanesulfonyl}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-(2-(4-tetradecyl-1-piperazine)-acetyl})))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1\text{-(4-tetradecyl-piperazine})))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1\text{-tetradecylamino}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-tetradecanoyl}), \beta\text{-}Ala^{37})hGLP\text{-}1(7\text{-}37)\text{-}OH$ or

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)\text{-}OH$,

or a pharmaceutically acceptable salt thereof .

More preferred of the immediately foregoing group of compounds is a compound of the formula:

$(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^8, \beta\text{-}Ala^{35})hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35}, Arg^{26}, Lys^{34}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$,

$(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}38)NH_2$,

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-decanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$, or

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$_\varepsilon$-tetradecanoyl),ß-Ala^{37})hGLP-1(7-37) -OH, or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is where said compound is of the formula:

(Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}; Arg^{26,34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-Aec-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH$_2$;

(Aib^{8,17,35},)hGLP-1(7-36)NH$_2$;

(Aib^{8} ,Arg^{26,34}, ß-Ala^{35}, D-Asp^{37}, Ava^{38}, Aun^{39})hGLP-1(7-39)NH$_2$;

(Gly^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Ser^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Glu^{22,23}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Gly^{8}, Aib^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{18}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{33}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{18}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH$_2$;

(Aib^{8,27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH$_2$;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH$_2$;

(Aib^{8}, Lys^{18,27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Arg^{38})hGLP-1(7-38)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35},)hGLP-1(7-36)NH_2;
(Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, ß-Ala^{35}, Arg^{37})hGLP-1(7-37)NH_2;
(Aib^{8}, Phe^{31}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36) NH_2;
(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(7-36)NH_2;
(Aib^{8},B-Ala^{35}, Ser^{37}(O-decanoyl))hGLP1(7-37)-NH_2;
(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38}, Lys^{39}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-39)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-37)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-37)NH_2; or
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-37)NH_2;
or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is each of the compounds that are specifically enumerated hereinbelow in the Examples section of the present disclosure, or a pharmaceutically acceptable salt thereof.

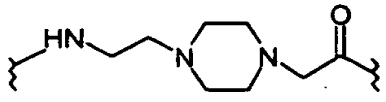
In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In yet another aspect, the present invention provides a method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes,

obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired, in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof. A preferred method of the immediately foregoing method is where the disease being treated is Type I diabetes or Type II diabetes.

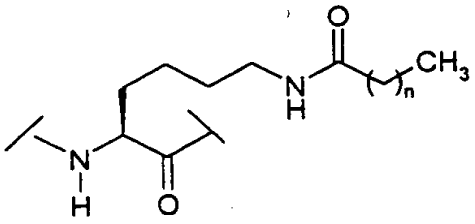
With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH_3 for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R^2R^3)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R^2 and R^3 are as defined above, except when A^7 is Ura, Paa or Pta, in which case R^2 and R^3 are not present since Ura, Paa and Pta are considered here as des-amino amino acids. Amp, ß-Nal, Nle, Cha, 3-Pal, 4-Pal and Aib are the abbreviations of the following α-amino acids: 4-amino-phenylalanine, ß-(2-naphthyl)alanine, norleucine, cyclohexylalanine, ß-(3-pyridinyl)alanine, ß-(4-pyridinyl)alanine and α-aminoisobutyric acid, respectively. Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α-aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α-aminoisobutyric acid; ß-Ala is ß-alanine; Gaba is γ-aminobutyric acid; Ava is 5-aminovaleric acid; Ado is 12-aminododecanoic acid, Aic is 2-aminoindane-2-carboxylic acid; Aun is 11-aminoundecanoic acid; and Aec is 4-(2-aminoethyl)-1-carboxymethyl-piperazine, represented by the structure:



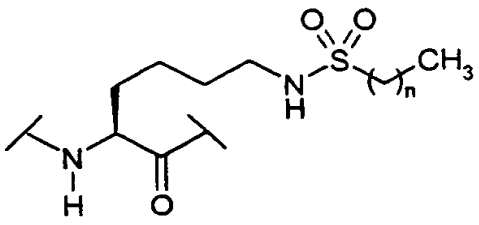
What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-

cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c). In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX^5 stands for $-C=O\cdot X^5$. Examples of $-C=O\cdot X^5$ include, but are not limited to, acetyl and phenylpropionyl.

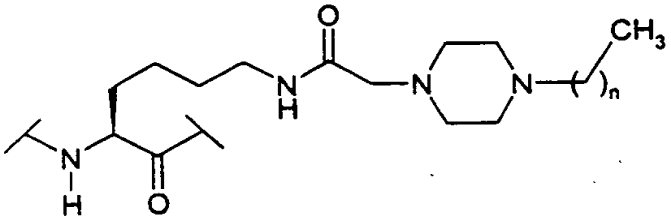
What is meant by Lys(N_ε-alkanoyl) is represented by the following structure:



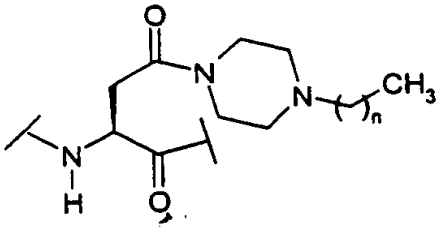
. What is meant by Lys(N_ε-alkylsulfonyl) is represented by the following structure:



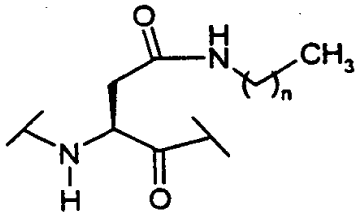
. What is meant by Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following structure:



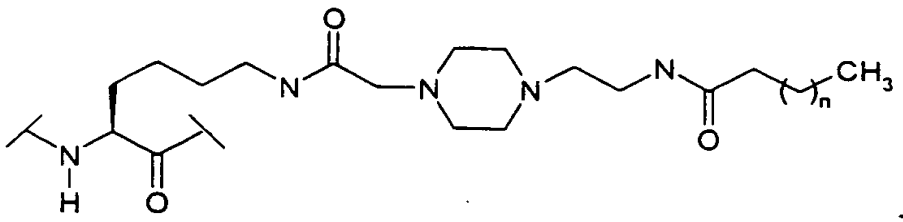
. What is meant by Asp(1-(4-alkyl-piperazine)) is represented by the following structure:



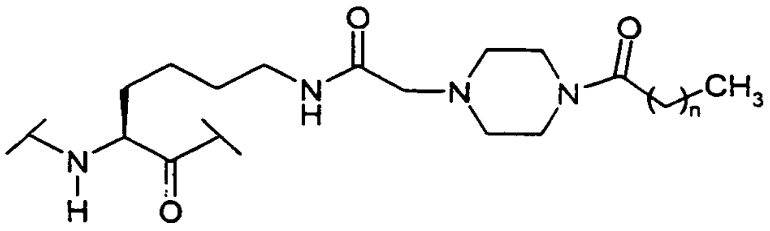
. What is meant by Asp(1-alkylamino) is represented by the following structure:



. What is meant by Lys(N_ε-Aec-alkanoyl) is r presented by the structure:



The variable n in the foregoing structures is 1-30. What is meant by Lys (Nε-ace-alkanoyl) is represented by the structure:



The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl, OcHex for O-cyclohexyl, Fmoc for 9-fluorenylmethoxycarbonyl, HOBt for N-hydroxybenzotriazole and PAM resin for 4-hydroxymethylphenylacetamidomethyl resin.

The term "halo" encompasses fluoro, chloro, bromo and iodo.

The term "(C_1-C_{30})hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl, and in the case of alkenyl and alkynyl there are C_2-C_{30}.

A peptide of this invention is also denoted herein by another format, e.g., (A5c^8)hGLP-1(7-36)NH_2, with the substituted amino acids from the natural sequence placed between the first set of parentheses (e.g., A5c^8 for Ala^8 in hGLP-1). The abbreviation GLP-1 means glucagon-like peptide-1; hGLP-1 means human glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequ nce for human GLP-1). Th sequence for hGLP-

1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res,. 40, 1992, pp. 333-342. The designation "NH_2" in hGLP-1(7-36)NH_2 indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid. In hGLP-1(7-38), residues in positions 37 and 38 are Gly and Arg, respectively.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R^2 and R^3 of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE^1, may be attached by coupling the free acid, e.g., E^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R^1 is NH-X^2-CH_2-$CONH_2$, (i.e., Z^0=$CONH_2$), the synthesis of the peptide starts with BocHN-X^2-CH_2-COOH which is coupled to the MBHA resin. If R^1 is NH-X^2-CH_2-COOH, (i.e., Z^0=COOH) the synthesis of the peptide starts with Boc-HN-X^2-CH_2-COOH which is coupled to PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X^2-COOH, HBTU and HOBt and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

The protected amino acid 1-(N-tert-butoxycarbonyl-amino)-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic layer was separated. The

aqueous layer was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. For the synthesis of (Tma-His^7)hGLP-1(7-36)NH_2, HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF are used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^1, can be attached by coupling the free acid, e.g., X^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidifed atmosphere of 5% CO_2/95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by

homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10 min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM $MgCl_2$, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM (^{125}I)GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound (^{125}I)GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total (^{125}I)GLP-1(7-36) bound minus that bound in the presence of 1000 nM GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous (See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536). Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis, neurodegenerative diseases, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of $1x10^{-7}$ to 200 mg/kg/day, preferably $1x10^{-4}$ to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating

agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbabl sustained release

compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

Boc-ßAla-OH, Boc-D-Arg(Tos)-OH and Boc-D-Asp(OcHex) were purchased from Nova Biochem, San Diego, California. Boc-Aun-OH was purchased from Bachem, King of Prussia, PA. Boc-Ava-OH and Boc-Ado-OH were purchased from Chem-Impex International, Wood Dale, IL. Boc-Nal-OH was purchased from Synthetech, Inc. Albany, OR.

Example 1

$(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$

The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnolzer, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.91 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The

synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2ClZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C_{18} column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer (MS(ES))S analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

Example 2

$((N_\alpha\text{-HEPES-His})^7, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$

The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after assembly of the peptide $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min.

After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 3

$((N_\alpha\text{-HEPA-His})^7, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$

The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making $((N_\alpha\text{-HEPES-His})^7, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Example 4

$(Aib^8, \beta\text{-}Ala^{35})hGLP\text{-}1(7\text{-}36)NH_2$

The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) gave the molecular weight at 3325.7, calculated MW = 3325.8, purity = 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ in Example 1 above, but using the appropriate protected amino acids depending on the desired peptide.

Example 5

$(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$

The Boc amino acids used were the same as those in the synthesis of $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ described in Example 1 except that Fmoc-Lys(Boc)-OH was used in this example. The first amino acid residue was coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the solution was then added 0.2 mmol of MBHA resin (substitution = 0.91 mmol/g). The mixture was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc

protecting group. The resin was washed with DMF. Myristic acid (2.5 mmol) was pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for 2 min and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin was washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The following steps synthesis and purification procedures for the peptide were the same as those in the synthesis of $(Aib^{8,35})$hGLP-1(7-36)NH_2 in Example 1. 43.1 mg of the title compound were obtained as a white solid. Purity was 98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3577.7 in agreement with the calculated molecular weight 3578.7.

Examples 6-8

Examples 6-8 were synthesized substantially according to the procedure described for Example 5 using the appropriate protected amino acid and the appropriate acid in place of the Myristic acid used in Example 5.

Example 6: $(Aib^{8,35}, Arg^{26}, Lys^{34}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-36)NH_2; Yield = 89.6 mg; MS(ES) = 3577.2, Calculated MW = 3578.7; Purity 96%.

Example 7: $(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-38)NH_2; Yield = 63.3 mg; MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

Example 8: $(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon$-decanoyl))hGLP-1(7-36)$NH_2$; Yield = 57.4 mg; MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

The syntheses of other compounds of the present invention containing Lys(N_ε-alkanoyl) residue can be carried out in an analogous manner to the procedure described for Example 5, $(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-36)NH_2. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N_ε-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N_ε-alkanoyl) residue is assembled on the resin on th peptide synthesizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 9

($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-dodecanesulfonyl))hGLP-1(7-36)NH_2

The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin(substitution = 0.91 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N_ε-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-alkylsulfonyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N_ε-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N_ε-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate akylsulfonyl chloride can be obtained from Lancaster Synthesis Inc., Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

Example 10

($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution =

0.91 mmol/g) resin. The mixtur is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. The 2-bromoacetic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as the procedures described for Example 1.

The syntheses of other compounds of the present invention containing Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is used for the residue of Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 11

(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH_2

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL

of DMF for about 15 min. 0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as those for the synthesis of Example 1.

The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used for the residue of Lys(N_ϵ-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is assembled on the resin on the peptide synthesizer first.

Example 12

($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-tetradecylamino))hGLP-1(7-36)NH_2

The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min. 0.6 mmol of 1-tetradecaneamin is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting gr up. The resin is washed with DMF and transferred to the reaction

vessel of the peptide synthesizer to continue the synth sis. The remaining synthesis and purification procedures for the peptide of this example are the same as those described for the synthesis of Example 1.

The syntheses of other compounds of the present invention containing Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

Example 13

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ϵ-tetradecanoyl),ß-Ala^{37})hGLP-1(7-37)-OH

The Boc amino acids used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ϵ-tetradecanoyl))hGLP-1(7-36)NH_2 (Example 5). 270 mg of Boc-ß-Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc-ß-Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

Example 14

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ϵ-tetradecanoyl))hGLP-1(7-36)-OH

The Boc amino acids to be used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ϵ-tetradecanoyl))hGLP-1(7-36)NH_2 (Example 5). Fmoc-Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBt (2.0 mmol and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5. Electro-spray mass spectrometer analysis gave the molecular weight at 3579.15 in agreement with the calculated weight 3579.5.

The syntheses of other analogs of hGLP-1(7-36)-OH, hGLP-1(7-37)-OH and hGLP-1(7-38)-OH of the instant invention which contain Lys(N_ε-alkanoyl) residue can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys.

Example 366

(Aib^8, ß-Ala^{35}, Aec^{37})hGLP-1(7-37)NH_2

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.40g, 0.829 mmol), HBTU (1.5 mL @ 0.5M in DMF) and DIEA (0.5mL) in a reaction vessel was shaken on a shaker for 4h at room temperature. The resin was then washed with DMF and treated with 25% piperidine in DMF for 2X20min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3494.8 in agreement with the calculated molecular weight 3494.99. Purity 93%; Yield 79.1mg.

Example 367

(Aib^8, ß-Ala^{35}, Aec^{38})hGLP-1(7-38)NH_2

Example 367 was synthesized substantially according to the procedure described for Example 366. MS(ES)=3551.7, calculated MW=3552.04; Purity 97%; Yield 97.4mg.

Example 368:

(Aib^8, ß-Ala^{35}, Aec^{37,38})hGLP-1(7-38)NH_2

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL) in a reaction vessel was shaken on a shaker for 2h at room temperature. The resin was then washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 2h. The resin was washed with DMF

and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3663.9 in agreement with the calculated molecular weight 3664.26. Purity 100%; Yield 75.3mg.

Example 369

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-Aec-decanoyl))hGLP-1(7-36)NH$_2$

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Boc-Lys(Fmoc)-OH (1.17g, 2.5mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) in a reaction vessel was shaken on a shaker at room temperature for 10min. The resin was washed with DMF and treated with 25% piperidine in DMF for 2X15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 10min. The resin was washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF and treated with a mixture of decanoic acid (431mg, 2.5 mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) for 10 min. The resin was washed with DMF and treated with 100% TFA for 2X2 min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3677.0 in agreement with the calculated molecular weight 3677.25. Purity 97.6%;Yield 44.8mg.

The following examples can be made according to the appropriate procedures described hereinabove.

Example 15: (Aib^{35})hGLP-1(7-36)NH$_2$

Example 16: (ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 17: ((N$^{\alpha}$-Me-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH$_2$

Example 18: ((N$^{\alpha}$-Me-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 19: ((N$^{\alpha}$-Me-His)^{7}, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH$_2$

Example 20: ((N$^{\alpha}$-Me-His)^{7}, Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 21: (Aib^{8}, A6c^{35})hGLP-1(7-36)NH_2

Example 22: (Aib^{8}, A5c^{35})hGLP-1(7-36)NH_2

Example 23: (Aib^{8}, D-Ala^{35})hGLP-1(7-36)NH_2

Example 24: (Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH_2

Example 25: (Aib^{8,35}, A5c^{32})hGLP-1(7-36)NH_2

Example 26: (Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH_2

Example 27: (Aib^{8,24,35})hGLP-1(7-36)NH_2

Example 28: (Aib^{8,30,35})hGLP-1(7-36)NH_2

Example 29: (Aib^{8,25,35})hGLP-1(7-36)NH_2

Example 30: (Aib^{8,35}, A6c^{16,20})hGLP-1(7-36)NH_2

Example 31: (Aib^{8,35}, A6c^{16,29,32})hGLP-1(7-36)NH_2

Example 32: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2

Example 33: (Aib^{8,35}, A6c^{20})hGLP-1(7-36)NH_2

Example 34: (Aib^{8,35}, Lys^{25})hGLP-1(7-36)NH_2

Example 35: (Aib^{8,24,35}, A6c^{20})hGLP-1(7-36)NH_2

Example 36: (Aib^{8,35}, A6c^{29,32})hGLP-1(7-36)NH_2

Example 37: (Aib^{8,24,35}, A6c^{29,32})hGLP-1(7-36)NH_2

Example 38: (Aib^{8,35}, A6c^{12})hGLP-1(7-36)NH_2

Example 39: (Aib^{8,35}, Cha^{20})hGLP-1(7-36)NH_2

Example 40: (Aib^{8,35}, A6c^{33})hGLP-1(7-36)NH_2

Example 41: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2

Example 42: (Aib^{8}, A6c^{16,20}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 43: (Aib^{8,35}, ß-Ala^{22})hGLP-1(7-36)NH_2

Example 44: (Aib^{8,22,35})hGLP-1(7-36)NH_2

Example 45: (Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2

Example 46: (Aib^{8,24,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2

Example 47: (Aib^{8,24,25,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2

Example 48: (Aib^{8,24,25,35}, A6c^{16,20,32}, Glu^{23})hGLP-1(7-36)NH_2

Example 49: (Aib^{8}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 50: (Aib^{8}, A5c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 51: (Aib^{8}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 52: (Aib^{8,24}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 53: (Aib^{8,30}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 54: (Aib^{8,25}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 55: (Aib^{8}, A6c^{16,20}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 56: (Aib^{8}, A6c^{16,29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 57: (Aib^{8}, A6c^{20,32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 58: (Aib^{8}, A6c^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 59: (Aib^{8}, Lys^{25}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 60: (Aib^{8,24}, A6c^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 61: (Aib^{8}, A6c^{29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 62: (Aib^{8,24}, A6c^{29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 63: (Aib^{8}, A6c^{12}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 64: (Aib^{8}, Cha^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 65: (Aib^{8} , A6c^{33}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 66: (Aib^{8}, A6c^{20,32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 67: (Aib^{8}, ß-Ala^{22,35})hGLP-1(7-36)NH_2

Example 68: (Aib^{8,22}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 69: (Aib^{8}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 70: (Aib^{8,24}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 71: (Aib^{8,24}, Glu^{23}, A6c^{32}, Lys^{34}(N_ε-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH_2

Example 72: (Aib^{8,24,25}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 73: (Aib^{8,24,25}, A6c^{16,20,32}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 74: (Aib^{8,35}, D-Arg^{36})hGLP-1(7-36)NH_2

Example 75: (Aib^{8,35}, D-Lys^{36})hGLP-1(7-36)NH_2

Example 76: (Aib^{8}, ß-Ala^{35}, D-Arg^{36})hGLP-1(7-36)NH_2

Example 77: (Aib^{8}, ß-Ala^{35}, D-Lys^{36})hGLP-1(7-36)NH_2

Example 78: (Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH_2

Example 79: (Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 80: (Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH_2

Example 81: (Aib^{8}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 82: (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-36)OH

Example 83: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-37)OH

Example 84: (Aib^{8,35,37}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-37)OH

Example 85: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl), D-Ala^{37})hGLP-1(7-37)OH

Example 86: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-38)OH

Example 87: (Aib^{8,35}, Arg^{26,34}, ß-Ala^{37}, Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-38)OH

Example 88: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)OH

Example 89: (Aib^{8}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{37})hGLP-1(7-37)OH

Example 90: (Aib^{8,37}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-37)OH

Example 91: (Aib^{8,35}, Arg^{26,34}, Ado^{37})hGLP-1(7-37)OH

Example 92: (Aib^{8,35}, Arg^{26,34}, Ado^{37})hGLP-1(7-37)NH$_2$

Example 93: (Aib^{8}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl), D-Ala^{37})hGLP-1(7-37)OH

Example 94: (Aib^{8,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)OH

Example 95: (Aib^{8}, Arg^{26,34}, ß-Ala^{37}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)OH

Example 96: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 97: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 98: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 99: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 100: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 101: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 102: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 103: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 104: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 105: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-decanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 106: (Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 107: (Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 108: (Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 109: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 110: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 111: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 112: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 113: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 114: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 115: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 116: (Aib^{8}, Lys^{26}(N$^{\varepsilon}$-decanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 117: (Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 118: (Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 119: (Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 120: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 121: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 122: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 123: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 124: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 125: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 126: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 127: (Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 128: (Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 129: (Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 130: (Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 131: (Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 132: (Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 133: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 134: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 135: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 136: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 137: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 138: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$

Example 139: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$

Example 140: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$

Example 141: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$

Example 142: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$

Example 143: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$

Example 144: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$

Example 145: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$

Example 146: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$

Example 147: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$

Example 148: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$

Example 149: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$

Example 150: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$

Example 151: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$

Example 152: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$

Example 153: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 154: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 155: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 156: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 157: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 158: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 159: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 160: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 161: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 162: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 163: (Aib^{8}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 164: (Aib^{8}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 165: (Aib^{8}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 166: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 167: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 168: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 169: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 170: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 171: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 172: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 173: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 174: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 175: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 176: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 177: (Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 178: (Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 179: (Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 180: (Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 181: (Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 182: (Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 183: (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 184: (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 185: (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$- hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 186: (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 187: (Aib^{8}, Lys^{25}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 188: (Aib^{8}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 189: (Aib^{8}, Lys^{25}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 190: (Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 191: (Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 192: (Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 193: (Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 194: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$

Example 195: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$

Example 196: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$

Example 197: (Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 198: (Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 199: (Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 200: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 201: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 202: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 203: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 204: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 205: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 206: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 207: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 208: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 209: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$

Example 210: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 211: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 212: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 213: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 214: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 215: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 216: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 217: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 218: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 219: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 220: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 221: (Aib^{8,24,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 222: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 223: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 224: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 225: (Aib^{8,35}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 226: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 227: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 228: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 229: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 230: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 231: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 232: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 233: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 234: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 235: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 236: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 237: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 238: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 239: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 240: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 241: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 242: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 243: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 244: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 245: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 246: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 247: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 248: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 249: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 250: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 251: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 252: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 253: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 254: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$

Example 255: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$

Example 256: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$

Example 257: ((N$^{\alpha}$-HEPES-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$

Example 258: ((N$^{\alpha}$-HEPES-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 259: ((N$^{\alpha}$-HEPES-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 260: ((N$^{\alpha}$-HEPA-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$

Example 261: ((N$^{\alpha}$-HEPA-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 262: ((N$^{\alpha}$-HEPA-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 263: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$

Example 264: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 265: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH$_2$

Example 266: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 267: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, Aib^{35})hGLP-1(7-36)NH$_2$

Example 268: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 269: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH$_2$

Example 270: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 271: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 272: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH$_2$

Example 273: ((N$^{\alpha}$-t tradecanoyl-His)^{7}, Aib^{8}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$

Example 274: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 275: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-dodecanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$

Example 276: (Aib^{8,35}, Lys^{26}(N^{ε}-hexadecanesulfonyl), Arg^{34})hGLP-1(7-36)NH_2

Example 277: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-octanesulfonyl))hGLP-1(7-36)NH_2

Example 278: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-dodecanesulfonyl))hGLP-1(7-36)NH_2

Example 279: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-hexadecanesulfonyl))hGLP-1(7-36)NH_2

Example 280: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-octanesulfonyl))hGLP-1(7-36)NH_2

Example 281: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N^{ε}-hexadecanesulfonyl))hGLP-1(7-36)NH_2

Example 282: (Aib^{8,35}, Asp^{26}(1-(4-decylpiperazine)), Arg^{34})hGLP-1(7-36)NH_2

Example 283: (Aib^{8,35}, Asp^{26}(1-(4-dodecylpiperazine)), Arg^{34})hGLP-1(7-36)NH_2

Example 284: (Aib^{8,35}, Asp^{26}(1-(4-tetradecylpiperazine)), Arg^{34})hGLP-1(7-36)NH_2

Example 285: (Aib^{8,35}, Asp^{26}(1-(4-hexadecylpiperazine)), Arg^{34})hGLP-1(7-36)NH_2

Example 286: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2

Example 287: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2

Example 288: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2

Example 289: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2

Example 290: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2

Example 291: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2

Example 292: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2

Example 293: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2

Example 294: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2

Example 295: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2

Example 296: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2

Example 297: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2

Example 298: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2

Example 299: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2

Example 300: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2

Example 301: (Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2

Example 302: (Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2

Example 303: (Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2

Example 304: (Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2

Example 305: (Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2

Example 306: (Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2

Exampl 307: (Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-tetradecylpiperazin)))hGLP-1(7-36)NH_2

Example 308: (Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2

Example 309: (Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2

Example 310: (Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2

Example 311: (Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2

Example 312: (Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2

Example 313: (Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2

Example 314: (Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2

Example 315: (Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2

Example 316: (Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2

Example 317: (Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2

Example 318: (Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2

Example 319: (Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2

Example 320: (Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2

Example 321: (Aib^{8,35}, Arg^{26,34}, Glu^{36}(1-dodecylamino))hGLP-1(7-36)NH_2

Example 322: (Aib^{8,35}, Glu^{26}(1-dodecylamino), Arg^{34})hGLP-1(7-36)NH_2

Example 323: (Aib^{8,35}, Arg^{26}, Glu^{34}(1-dodecylamino))hGLP-1(7-36)NH_2

Example 324: (Aib^{8,35,37}, Arg^{26,34}, Glu^{38}(1-dodecylamino))hGLP-1(7-38)NH_2

Example 325: (Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 326: (Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 327: (Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 328: (Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 329: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 330: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-dodecyl-1-piperazine)-acetyl))hGLP-1(7-36)NH_2

Example 331: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 332: (Aib^{8,35}, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 333: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 334: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 335: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 336: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 337: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 338: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 339: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 340: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 341: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 342: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 343: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 344: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 345: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 346: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 347: Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 348: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 349: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 350: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 351: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 352: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 353: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 354: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 355: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

Example 356: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 357: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 358: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 359: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 360: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 361: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 362: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 363: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2

Example 364: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH

Example 365: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH

Example 370 (Aib^{8,35},Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH_2

Example 371 (Aib^{8,35},Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH_2

Example 372 (Aib^{8,35},Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH_2

Example 373 (Aib^{8,17,35},)hGLP-1(7-36)NH_2

Example 374 (Aib^{8} ,Arg^{26,34}, ß-Ala^{35}, D-Asp^{37}, Ava^{38}, Aun^{39})hGLP-1(7-39)NH_2

Example 375 (Gly^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 376 (Ser^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 377 (Aib^{8}, Glu^{22,23}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 378 (Gly^{8}, Aib^{35})hGLP-1(7-36)NH_2

Example 379 (Aib^{8}, Lys^{18}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 380 (Aib^{8}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 381 (Aib^{8}, Lys^{33}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 382 (Aib^{8}, Lys^{18}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 383 (Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH_2

Example 384 (Aib^{8}, ß-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH_2

Example 385 (Aib^{8,27}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 386 (Aib^{8,27}, ß-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH_2

Example 387 (Aib^{8,27}, ß-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH_2

Example 388 (Aib^{8}, Lys^{18,27}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 389 (Aib^{8}, Lys^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 390 (Aib^{8}, ß-Ala^{35}, Arg^{38})hGLP-1(7-38)NH_2

Example 391 (Aib^{8}, Arg^{26,34}, ß-Ala^{35},)hGLP-1(7-36)NH_2

Example 392 (Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH_2

Example 393 (Aib^{8}, ß-Ala^{35}, Arg^{37})hGLP-1(7-37)NH_2

Example 394 (Aib^{8}, Phe^{31}, ß-Ala^{35})hGLP-1(7-36)NH_2

Example 395 (Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH_2

Example 396 (Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH_2

Example 397 (Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH_2

Example 398 (Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH_2

Example 399 (Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH_2

Example 400 (Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2

Example 401 (Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2

Example 402 (Aib^{8,35}, Lys^{36}(N^{ε}-decanoyl))hGLP-1(7-36) NH_2

Example 403 (Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2

Example 404 (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-dodecanoyl))hGLP-1(7-36)NH_2

Example 405 (Aib^{8},B-Ala^{35},Ser^{37}(O-decanoyl))hGLP1(7-37)-NH_2

Example 406 (Aib^{8,27}, ß-Ala^{35,37}, Arg^{38}, Lys^{39}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-39)NH_2

Example 407 (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-37)NH_2

Example 408 (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-37)NH_2

Example 409 (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-37)NH_2

Example 410 (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(7-37)NH_2

Example 411 (Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(8-37)NH_2

Physical data for a representative sampling of the compounds exemplified herein are given in Table 1.

Example Number	Mol. Wt. Expected	Mol. Wt. MS(ES)	Purity (HPLC)
24	3351.8	3352.2	88%
26	3340.17	3340.9	99%
27	3353.81	3353.9	99%
29	3353.81	3353.9	99%
45	3352.6	3352.5	97%
51	3326.74	3326.6	99%
78	3395.81	3395.5	96%
136	3494	3494	99%
364	3523.02	3523.6	99%
365	3580.13	3580.3	95%
369	3677.25	3677	97%
370	3692.28	3692.4	98%
371	3807.37	3807.3	98%
372	3579.11	3579.7	97.90%
373	3337.81	3338.5	94%
374	3779.3	3779.5	94%
375	3297.7	3297.5	99%
376	3327.7	3327.4	98%
377	3398.8	3398.7	97.50%
378	3311.6	3311	93%
379	3366.85	3366.5	97%
380	3309.8	3309.4	99%
381	3354.8	3354.5	97.70%
382	3350.9	3350.3	97.20%
383	3311.73	3310.7	92%
384	3481.95	3481.3	94.30%
385	3281.76	3281.6	98%
386	3509.02	3509.1	99.40%
387	3665.2	3665.1	99%
388	3365.91	3365	97%
389	3324.79	3324.2	95%
390	3539	3539.2	93%
391	3381.74	3381.3	97%

392	3410.89	3409.8	99%
393	3481.95	3481.1	90%
394	3286.76	3286.2	99.20%
395	3300.76	3299.4	93%
396	3350.81	3349.4	99%
397	3400.87	3400.1	99%
398	3406.84	3406.4	99%
399	3356.77	3356.6	99%
400	3384.87	3384.43	94%
401	3400.87	3401.3	99%
402	3466.03	3466.9	97.40%
403	3522.05	3522.06	93%
404	3550.11	3550.2	98%
405	3567.09		99%
406	3763.38	3763.2	95%
407	3636.15	3635.8	99%
408	3664.21	3663.3	99%
409	3720.32	3719.5	99%
410	3692.27	3691.7	99%
411	3555.13	3554.4	99%

TABLE 1

CLAIMS

What is claimed is:

1. A compound of formula (I),

(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, ß-Nal, Cha, Trp or X^1-Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, ß-Nal or X^1-Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1-Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-$N(R^{10}R^{11})$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-$N(R^{10}R^{11})$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Ph , Pal, ß-Nal, X^1-Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, ß-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X^1-Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or X^1-Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is Gly, ß-Ala, D-Ala, Gaba, Ava, HN-$(CH_2)_m$-C(O), Aib, Acc or a D-amino acid;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

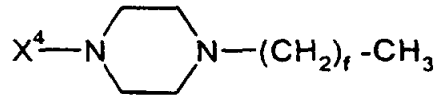
A^{37} is Gly, ß-Ala, Gaba, Ava, Aib, Acc, Ado, Arg, Asp, Aun, Aec, HN-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), a D-amino acid, or deleted;

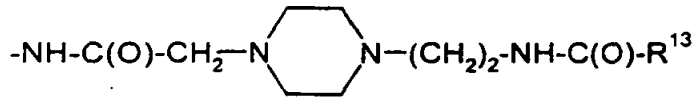
A^{38} is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) Ava, Ado, Aec or deleted;

A^{39} is D- or L-Lys, D- or L-Arg, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), Ava, Ado, or Aec;

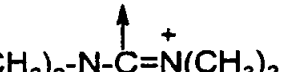
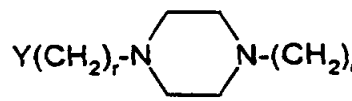
X^1 for each occurrence is independently selected from the group consisting of (C_1-C_6)alkyl, OH and halo;

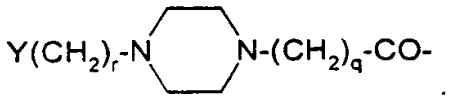
R^1 is OH, NH_2, (C_1-C_{30})alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a (C_1-C_{12})hydrocarbon moiety, and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is 



or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is  , (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, C(O)X^5,  , or



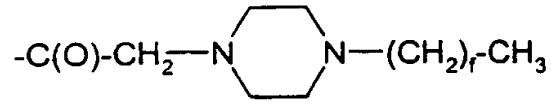
; wherein Y is H, OH or NH_2; r is 0 to 4; q is 0 to 4; and X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl or hydroxynaphthyl(C_1-C_{30})alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, (C_1-C_{30})alkyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, $-C((NH)(NH_2))$ or



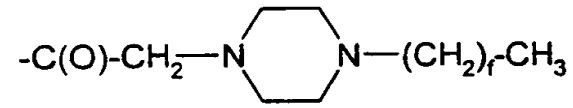
; and

R^{12} and R^{13} each is, independently for each occurrence, (C_1-C_{30})alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, $-C((NH)(NH_2))$ or



, then R^{11} is H or (C_1-C_{30})alkyl;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not ($Arg^{26,34}$, Lys^{38})hGLP-1(7-38)-E, (Lys^{26}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, (Lys^{34}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, ($Lys^{26,34}$-bis(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E, (Arg^{26}, Lys^{34}(N_ε-alkanoyl))hGLP-1(8-36, -37 or -38)-E, ($Arg^{26,34}$, Lys^{36}(N_ε-alkanoyl))hGLP-1(7-36, -37 or –38)-E or ($Arg^{26,34}$, Lys^{38}(N_ε-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or $-NH_2$;

(iv) a compound of formula (I) is not Z^1-hGLP-1(7-36, -37 or -38)-OH, Z^1-hGLP-1(7-36, -37 or -38)-NH_2, wherein Z^1 is selected from the group consisting of:

(e) (Arg^{23}), (Arg^{34}), ($Arg^{26,34}$), (Lys^{38}), (Arg^{26}, Lys^{36}), (Arg^{34}, Lys^{36}), (D-Lys^{36}), (Arg^{35}), (D-Arg^{36}), ($Arg^{26,34}$, Lys^{36}) or ($Arg^{26,36}$, Lys^{34});

(f) (Asp^{21});

(g) at least one of (Aib^8), (D-Ala^8) and (Asp^9); and

(h) (Tyr^7), (N-acyl-His^7), (N-alkyl-His^7), (N-acyl-D-His^7) or (N-alkyl-D-His^7);

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not (N-Me-Ala^8)hGLP-1(8-36 or -37), (Glu^{15})hGLP-1(7-36 or -37), (Asp^{21})hGLP-1(7-36 or -37) or (Phe^{31})hGLP-1(7-36 or -37)

or a pharmaceutically acceptable salt thereof.

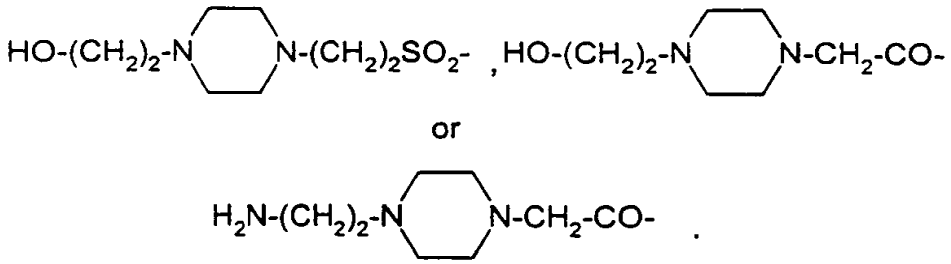
2. A compound according to claim 1, wherein A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu; and A^{31} is Trp; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O); A^{28} is Phe; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val or Acc; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3, wherein A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c or Gly; and A^{37} is Gly, Aib, ß-Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

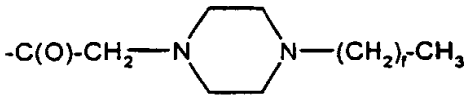
5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R^1 is OH or NH_2.

6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^2 is H and R^3 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl,



or

7. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or



, and R^{11} is H.

8. A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alkylsulfonyl or

9. A compound according to claim 1 wherein said compound is

($Aib^{8,35}$)hGLP-1(7-36)NH_2,

((N_α-HEPES-His)^7, $Aib^{8,35}$)hGLP-1(7-36)NH_2,

((N_α-HEPA-His)^7, $Aib^{8,35}$)hGLP-1(7-36)NH_2,

(Aib^8, ß-Ala^{35})hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, Arg^{26}, Lys^{34}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2,

($Aib^{8,35,37}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-38)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-decanoyl))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-dodecanesulfonyl))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-tetradecylamino))hGLP-1(7-36)NH_2,

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl),ß-Ala^{37})hGLP-1(7-37)-OH or

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-36)-OH, or a pharmaceutically acceptabl salt thereof.

10. A compound according to claim 9 wherein said compound is

($Aib^{8,35}$)hGLP-1(7-36)NH_2,

(Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2,

(Aib^{8,35}, Arg^{26}, Lys^{34}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2,

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_ε-tetradecanoyl))hGLP-1(7-38)NH_2,

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ε-decanoyl))hGLP-1(7-36)NH_2, or

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ε-tetradecanoyl),ß-Ala^{37})hGLP-1(7-37)-OH, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

12. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

13. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

14. A method according to claim 13 wherein said disease is Type I diabetes or Type II diabetes.

15. A compound according to claim 1 wherein said compound is

(Aib^{35})hGLP-1(7-36)NH_2;

(ß-Ala^{35})hGLP-1(7-36)NH_2;

((N^{α}-Me-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH_2;

((N^{α}-Me-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2;

((N^{α}-Me-His)^{7}, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH_2;

((N^{α}-Me-His)^{7}, Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, A6c^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, A5c^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, D-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH_2;

(Aib^{8,35}, A5c^{32})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH_2;

(Aib^{8,24,35})hGLP-1(7-36)NH_2;
(Aib^{8,30,35})hGLP-1(7-36)NH_2;
(Aib^{8,25,35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{16,20})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{16,29,32})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{20})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Lys^{25})hGLP-1(7-36)NH_2;
(Aib^{8,24,35}, A6c^{20})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{29,32})hGLP-1(7-36)NH_2;
(Aib^{8,24,35}, A6c^{29,32})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{12})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Cha^{20})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{33})hGLP-1(7-36)NH_2;
(Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{16,20}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, ß-Ala^{22})hGLP-1(7-36)NH_2;
(Aib^{8,22,35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2;
(Aib^{8,24,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2;
(Aib^{8,24,25,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2;
(Aib^{8,24,25,35}, A6c^{16,20,32}, Glu^{23})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, A5c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,24}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,30}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,25}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{16,20}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{16,29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{20,32}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, A6c^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, Lys^{25}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,24}, A6c^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, A6c^{29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,24}, A6c^{29,32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, A6c^{12}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Cha^{20}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8} , A6c^{33}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, A6c^{20,32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, ß-Ala^{22,35})hGLP-1(7-36)NH_2;

(Aib^{8,22}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,24}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,24}, Glu^{23}, A6c^{32}, Lys^{34}(N_ε-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,24,25}, Glu^{23}, A6c^{32}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,24,25}, A6c^{16,20,32}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,35}, D-Arg^{36})hGLP-1(7-36)NH_2;

(Aib^{8,35}, D-Lys^{36})hGLP-1(7-36)NH_2;

(Aib^{8}, ß-Ala^{35}, D-Arg^{36})hGLP-1(7-36)NH_2;

(Aib^{8}, ß-Ala^{35}, D-Lys^{36})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH_2;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH_2;

(Aib^{8}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-37)OH;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-37)OH;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl), D-Ala^{37})hGLP-1(7-37)OH;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8,35}, Arg^{26,34}, ß-Ala^{37}„Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N^{ε}-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl), ß-Ala^{37})hGLP-1(7-37)OH;

(Aib^{8,37}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-37)OH;

(Aib^{8,35}, Arg^{26,34}, Ado^{37})hGLP-1(7-37)OH;

(Aib^{8,35}, Arg^{26,34}, Ado^{37})hGLP-1(7-37)NH_2;

(Aib^{8}, Arg^{26,34}, Lys^{36}(N^{ε}-tetradecanoyl), D-Ala^{37})hGLP-1(7-37)OH;

(Aib^{8,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8}, Arg^{26,34}, ß-Ala^{37}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-decanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{25}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{26}(N$^{\varepsilon}$-decanoyl), Arg^{34}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-d canoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$- hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl), ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{25}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8}, Arg^{25,26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), A6c^{32}, Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPES-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPES-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPES-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPA-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPA-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-HEPA-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, Aib^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, Arg^{26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH$_2$;

((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, Arg^{25,26,34}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-dodecanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanesulfonyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-dodecanesulfonyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanesulfonyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanesulfonyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanesulfonyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Asp^{26}(1-(4-decylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Asp^{26}(1-(4-dodecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Asp^{26}(1-(4-tetradecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Asp^{26}(1-(4-hexadecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26}, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35}, Arg^{25,26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{25,26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{26,34}, Glu^{36}(1-dodecylamino))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Glu^{26}(1-dodecylamino), Arg^{34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Glu^{34}(1-dodecylamino))hGLP-1(7-36)NH_2;

(Aib^{8,35,37}, Arg^{26,34}, Glu^{36}(1-dodecylamino))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazin)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{25,26,34} , Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35},Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH_2;

(Aib^{8,35},Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH_2;

(Aib^{8,35},Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH_2;

(Aib^{8,17,35},)hGLP-1(7-36)NH_2;

(Aib^{8} ,Arg^{26,34}, ß-Ala^{35}, D-Asp^{37}, Ava^{38}, Aun^{39})hGLP-1(7-39)NH_2;

(Gly^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Ser^{8}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Glu^{22,23}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Gly^{8}, Aib^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{18}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{33}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, Lys^{18}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH_2;

(Aib^{8}, ß-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH_2;

(Aib^{8,27}, ß-Ala^{35})hGLP-1(7-36)NH_2;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH_2;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH_2;
(Aib^{8}, Lys^{18,27}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, Lys^{27}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, ß-Ala^{35}, Arg^{38})hGLP-1(7-38)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35},)hGLP-1(7-36)NH_2;
(Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH_2;
(Aib^{8}, ß-Ala^{35}, Arg^{37})hGLP-1(7-37)NH_2;
(Aib^{8}, Phe^{31}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Lys^{36}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-dodecanoyl))hGLP-1(7-36)NH_2;
(Aib^{8},B-Ala^{35},Ser^{37}(O-decanoyl))hGLP1(7-37)-NH_2;
(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38}, Lys^{39}(N^{ε}-octanoyl))hGLP-1(7-39)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-octanoyl))hGLP-1(7-37)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-decanoyl))hGLP-1(7-37)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-tetradecanoyl))hGLP-1(7-37)NH_2;
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-dodecanoyl))hGLP-1(7-37)NH_2; or
(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-dodecanoyl))hGLP-1(8-37)NH_2;
or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15 wherein said compound is
(Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH_2;
(Aib^{8,24,35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2;
(Aib^{8}, Glu^{23}, ß-Ala^{35})hGLP-1(7-36)NH_2;
(Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-Aec-decanoyl))hGLP-1(7-36)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH$_2$;

(Aib^{8,35},Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH$_2$;

(Aib^{8,17,35},)hGLP-1(7-36)NH$_2$;

(Aib^{8} ,Arg^{26,34}, ß-Ala^{35}, D-Asp^{37}, Ava^{38}, Aun^{39})hGLP-1(7-39)NH$_2$;

(Gly^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Ser^{8}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Glu^{22,23}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Gly^{8}, Aib^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{18}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{33}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{18}, Leu^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH$_2$;

(Aib^{8,27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH$_2$;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH$_2$;

(Aib^{8}, Lys^{18,27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, Lys^{27}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Arg^{38})hGLP-1(7-38)NH$_2$;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35},)hGLP-1(7-36)NH$_2$;

(Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8}, ß-Ala^{35}, Arg^{37})hGLP-1(7-37)NH$_2$;

(Aib^{8}, Phe^{31}, ß-Ala^{35})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH$_2$;

(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2;

(Aib^{8,35}, Lys^{36}(N^{ε}-decanoyl))hGLP-1(7-36) NH_2;

(Aib^{8,35}, Arg^{34}, Lys^{26}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2;

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^{ε}-dodecanoyl))hGLP-1(7-36)NH_2;

(Aib^{8},B-Ala^{35}, Ser^{37}(O-decanoyl))hGLP1(7-37)-NH_2;

(Aib^{8,27}, ß-Ala^{35,37}, Arg^{38}, Lys^{39}(N^{ε}-octanoyl))hGLP-1(7-39)NH_2;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-octanoyl))hGLP-1(7-37)NH_2;

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-decanoyl))hGLP-1(7-37)NH_2; or

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{37}(N^{ε}-tetradecanoyl))hGLP-1(7-37)NH_2;

or a pharmaceutically acceptable salt thereof.

17. Use of a compound as claimed in any of claims 1 to 10, or 15 or 16, in the preparation of a medicament for the treatment of disease.

18. Use as claimed in claim 17, in which the disease is selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease.

INTE IATIONAL SEARCH REPORT

[redacted] rnational Application No
[redacted] T/EP 99/09660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/605 A61K38/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, BIOTECHNOLOGY ABS, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 19698 A (LILLY CO ELI) 14 May 1998 (1998-05-14) the whole document, especially page 10, lines 5-16 ---	1
X	WO 91 11457 A (BUCKLEY DOUGLAS I ;HABENER JOEL F (US); MALLORY JOANNE B (US); MOJ) 8 August 1991 (1991-08-08) page 5, line 17 - line 20 page 5, line 29 - line 31 page 20, line 33 -page 21, line 27 page 24, line 31 - line 33 page 25, line 17 - line 22 ---	1
A	-/--	2-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2000	22. 8. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Kok, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PARKER J C ET AL: "STRUCTURE-FUNCTION ANALYSIS OF A SERIES OF GLUCAGON-LIKE PEPTIDE-1 ANALOGS" JOURNAL OF PEPTIDE RESEARCH,DK,MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, vol. 52, no. 5, 1 November 1998 (1998-11-01), pages 398-409, XP000788444 ISSN: 1397-002X the whole document	1-17
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